

APPROVAL ALERT

Zolbetuximab's Impact on Gastric/GEJ Adenocarcinoma

John Marshall, MD, sat down with CancerNetwork to review zolbetuximab-clzb, which the FDA recently approved for patients with claudin 18.2 (CLDN18.2)–positive locally advanced unresectable or metastatic HER2-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma. The therapy was approved in combination with fluoropyrimidine- and platinum-containing chemotherapy.¹

Marshall is the physician executive director of MedStart Washington DC Integrated Hematology-Oncology Division, director of the Ruesch Center for the Cure of Gastrointestinal Cancers, Frederick P. Smith Endowed Chair, and chief medical officer at Georgetown University Lombardi Comprehensive Cancer Center in Washington, DC. He explained that although zolbetuximab is helping to improve an unmet need, there are still many obstacles to overcome in the treatment of patients with gastric/GEJ adenocarcinoma.

Q / How has the FDA approval of zolbetuximab affected patients with locally advanced or unresectable CLDN18.2-positive gastric or gastroesophageal adenocarcinoma?

Marshall / In GI [gastrointestinal] cancers, we have been longing for new targets. We have been longing for new therapies. Finally, we are getting one. CLDN18.2 has been out there for a while, and drug development targeting this has been going on for a while. Two big randomized studies now support the benefit [of zolbetuximab] in this patient population. Now we [have] the drug [approval]. We have been delayed by some other issues that have slowed the approvals, but we are excited, and we are all looking forward to incorporating [zolbetuximab] into our treatment paradigm.

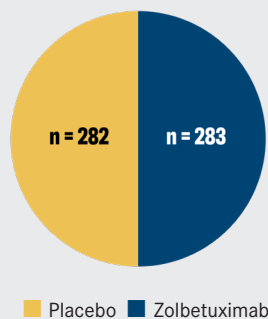
Q / What is your impression of the SPOTLIGHT (NCT03504397) and GLOW trial results (NCT03653507)?^{2,3}

Marshall / These 2 big phase 3 studies demonstrate [support for the approval] and took patients with gastric and GEJ

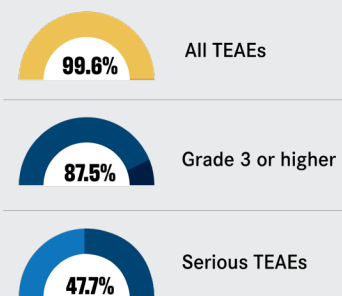
STATS AT A GLANCE

SPOTLIGHT Data²

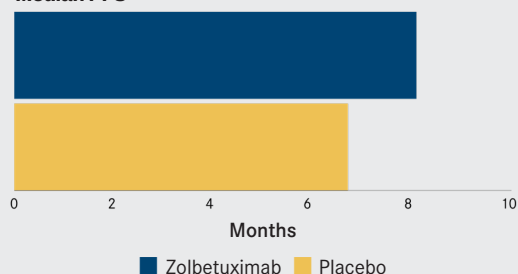
Patient population



Adverse effects



Median PFS



PFS, progression-free survival; TEAE, treatment-emergent adverse effect.

STATS AT A GLANCE

GLOW Data³

cancers and measured their CLDN18.2 expression. [Approximately] 40% had high enough levels to be involved [in the studies].... One of the studies was using traditional chemotherapy, and the other [used] capecitabine-based therapy; [these were] essentially the same trial, with 2 different backbones of fluoropyrimidine. Both of them demonstrated an improved progression-free and overall survival [with zolbetuximab]. Based on [the findings], we are hoping to get this approval.

It is important to note that there was not a big delta in response rate, which surprised us; there was some delta, but not a big delta. It is doing something to the biology of this patient population. The one thing that will be confusing to us as clinicians is what to do for a patient [whose disease] is PD-L1 positive and CLDN18.2 positive. Do you bring immunotherapy in? Right now, the preliminary data suggest that most of the patients who [have CLDN18.2-positive disease] also have low PD-L1 [expression]. That might help our decision-making as to what targeted therapy to bring to the table, but that will be the biggest decision tree we will have going forward.

Q / What unmet need would this approval help reduce?

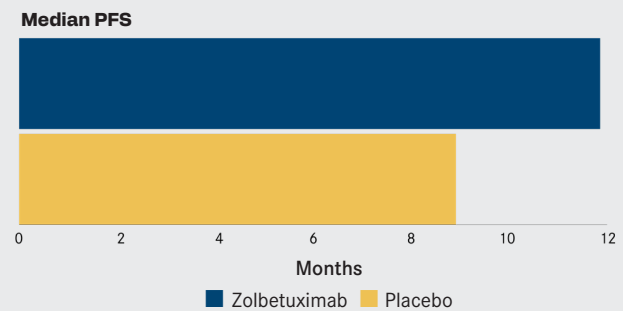
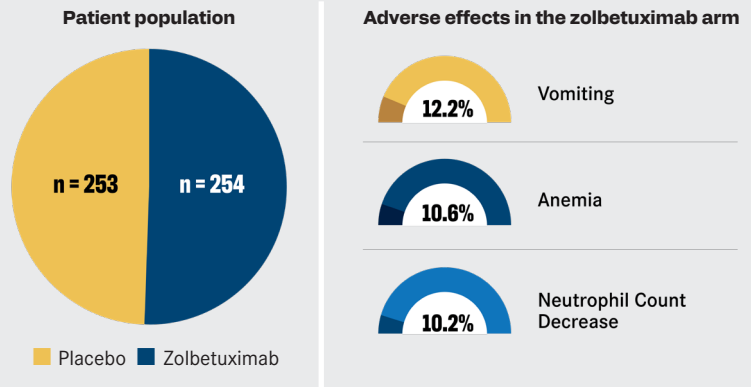
Marshall / Let's not forget our goal here. The unmet need is [enormous]. You can't imagine how much need we have, and each of these therapies is 1 step on a very long staircase. We need [zolbetuximab]. We need to include [zolbetuximab]. It will improve outcomes for a select group of patients, but we need more [options].

Q / How will this regimen be implemented into clinical practice?

Marshall / The next steps are, how do we take this new tool in the toolbox and leverage it to get even more benefit? It's clear that the clinical data will support this. The biggest need will be that doctors need to start testing for [CLDN18.2]. It's not in our routine to test for CLDN, and that's going to be the biggest new thing that's going to happen across the country.

Q / Are there any toxicities with the zolbetuximab regimen that stand out to you?

Marshall / When you combine this drug with chemotherapy, there is an increase in nausea, vomiting, and a little bit of appetite loss. There is a GI effect, and we will learn to manage and dose



PFS, progression-free survival.

appropriately to get around that, but it's certainly not an unmanageable toxicity.

Q / What other developments in GI cancers have the potential to change clinical practice?

Marshall / We are increasingly understanding that gastric cancer is more than 1 disease. It is molecularly broken out into different subgroups, and depending on the molecular subgroups, we have different treatment algorithms. We are beginning to gain knowledge that I believe, over time, is going to continue to improve outcomes. As with many of the GI cancers, we still have a long road [ahead] to understand how to better manage this cancer [type]. I am hopeful that with improvements in our understanding of immunotherapy approaches, [and with] more precision medicine targets and therapies, we will see the robust improvements that we need.

The biggest thing that we need to do as clinicians is begin to incorporate CLDN18.2 testing for our patients. We are not incorporating fast enough the molecular testing that is required based on the speed of development. If you have a [patient with] gastric cancer [for whom] you do HER2 testing and microsatellite instability [testing], you also now have to do CLDN18.2 [testing]. ■

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